General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing.

Bibliographic Source(s)

Martin MA, Klein TE, Dong BJ, Pirmohamed M, Haas DW, Kroetz DL, Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing. Clin Pharmacol Ther. 2012 Apr;91(4):734-8. [40 references] PubMed

Guideline Status

This is the current release of the guideline.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) reaffirmed the currency of this guideline in 2014.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Genetic Test Interpretation

The assignment of the likely human leukocyte antigen B (HLA-B) phenotype, based on allele diplotypes, is summarized in Table 1 below.

Table 1. Assignment of Likely HLA-B Phenotypes Based on Genotypes

Likely Phenotype	Genotypes	Examples of Diplotypes
Very low risk of hypersensitivity (constitutes ~94%[a] of patients)	Absence of **57:01* alleles (reported as "negative" on a genotyping test)	*X/*X[b]
High risk of hypersensitivity (~6% of patients)	Presence of at least one **57:01* allele (reported as "positive" on a genotyping test)	*57:01/*X[b] *57:01/*57:01

[a]See Supplementary Data (see the "Availability of Companion Documents" field) for estimates of genotype frequencies among different ethnic/geographic groups.

[b]*X = any *HLA-B* genotype other than **57:01*.

Therapeutic Recommendations

The guideline authors agree with others that *HLA-B*57:01* screening should be performed in all abacavir-naive individuals before initiation of abacavir-containing therapy (see the table below); this is consistent with the recommendations of the U.S. Food and Drug Administration, the U.S. Department of Health and Human Services, and the European Medicines Agency. In abacavir-naive individuals who are *HLA-B*57:01*-positive, abacavir is not recommended and should be considered only under exceptional circumstances when the potential benefit, based on resistance patterns and treatment history, outweighs the risk. *HLA-B*57:01* genotyping is widely available in the developed world and is considered the standard of care prior to initiating abacavir. Where *HLA-B*57:01* genotyping is not clinically available (such as in resource-limited settings), some have advocated initiating abacavir, provided there is appropriate clinical monitoring and patient counseling about the signs and symptoms of hypersensitivity reaction (HSR), although this remains at the clinician's discretion.

There is some debate among clinicians regarding whether *HLA-B*57:01* testing is necessary in patients who had previously tolerated abacavir chronically, discontinued its use for reasons other than HSR, and are now planning to resume abacavir. The presence of *HLA-B*57:01* has a positive predictive value of ~50% for immunologically confirmed hypersensitivity, indicating that some *HLA-B*57:01*-positive individuals can be, and have been, safely treated with abacavir. However, the guideline authors were unable to find any data to show that *HLA-B*57:01*-positive individuals with previous, safe exposure to abacavir had zero risk of HSR upon re-exposure. Although there are isolated case reports of previously asymptomatic patients developing a hypersensitivity-like reaction after restarting abacavir, there were confounding circumstances. Many of the patients had complicating concomitant illnesses that could have masked an HSR during initial abacavir therapy, and none were immunologically confirmed, making the case reports difficult to interpret. Furthermore, most of these case reports precede the availability of *HLA-B*57:01* genetic testing, making it impossible to determine from the published data whether there could be a risk of HSR upon re-exposure to abacavir in previously asymptomatic *HLA-B*57:01*-positive patients.

In addition, there may also exist a small group of patients who have been on chronic abacavir therapy since before the introduction of *HLA-B*57:01* genotyping. Given that virtually all abacavir HSR events occur within the first several weeks of therapy, and that ~50% of *HLA-B*57:01* carriers can safely take abacavir, the guideline authors were unable to find any evidence to suggest that *HLA-B*57:01*-positive individuals on current, long-term, uninterrupted abacavir therapy are at risk of developing HSR. Existing clinical guidelines have a blanket recommendation that all *HLA-B*57:01*-positive individuals should avoid abacavir, regardless of patient history. Although *HLA-B*57:01* genotyping has proven utility in significantly reducing the incidence of both clinically diagnosed and immunologically confirmed hypersensitivity in patients being newly considered for abacavir therapy, the connection between *HLA-B*57:01* genotype and risk of HSR in patients with previous asymptomatic abacavir use is less clear.

Recommendations for Incidental Findings

Although other variants in *HLA-B* are associated with autoimmune diseases and drug response phenotypes, they have not been associated with abacavir HSR.

Other Considerations

Abacavir skin patch testing may be performed after a case of clinically diagnosed HSR to determine whether it can be immunologically confirmed. At this time, skin patch testing is an investigational procedure, and the results should be interpreted only by an experienced immunologist. More details on skin patch testing can be found in the Supplementary Materials and Methods online (see the "Availability of Companion Documents" field).

Table 2. Recommended Therapeutic Use of Abacavir in Relation to *HLA-B* Genotype

Genotype	Implications for Phenotypic Measures	Recommendations for Abacavir	Classification of Recommendations
Noncarrier of *HLA-B*57:01*	Low or reduced risk of abacavir hypersensitivity	Use abacavir per standard dosing guidelines	Strong
Carrier of *HLA-B*57:01*	Significantly increased risk of abacavir hypersensitivity	Abacavir is not recommended	Strong

HLA-B, human leukocyte antigen B

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

The original guideline document includes a treatment algorithm for clinical use of abacavir based on *human leukocyte antigen B (HLA-B)*57:01* genotype.

Scope

Disease/Condition(s)

Human immunodeficiency virus (HIV) infection

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Internal Medicine

Medical Genetics

Pharmacology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information that will allow the interpretation of clinical *human leukocyte antigen B (HLA-B)* genotype tests so that the results can be

used to guide the use of abacavir for the treatment of human immunodeficiency virus (HIV)

Target Population

Individuals infected with human immunodeficiency virus (HIV)

Interventions and Practices Considered

Abacavir therapy based on *human leukocyte antigen B (HLA-B)*57:01* genotype

Major Outcomes Considered

- Risk of abacavir hypersensitivity
- Positive predictive value and negative predictive value of genetic testing

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

2012 Original Guideline

The guideline authors searched the PubMed database (1966 to April 2011) and Ovid MEDLINE (1950 to April 2011) for keywords ((HLA OR HLA-B OR HLA-B57 OR HLA-B*5701) AND (abacavir)), as well as a more general search for (abacavir hypersensitivity).

To construct a *human leukocyte antigen B (HLA-B)*57:01* minor allele frequency table based on ethnicity, the PubMed® database (1966 to April 2011) and Ovid MEDLINE (1950 to April 2011) were searched using the following criteria: ((HLA-B OR HLA-B57 OR HLA-B*5701) AND (genotype OR allele OR frequency)) with filter limits set to retrieve "full-text" and "English" literature. Studies were considered for inclusion if (1) the ethnicity of the population was clearly indicated; (2) either allele frequencies or alleles for *HLA-B*57:01* genotypes were reported; (3) the method by which *HLA-B* was genotyped was reliable and proven (no proof-of-principle experiments); (4) the sample population consisted of at least 50 individuals; (5) the study represented publication of novel data (no reviews or meta-analyses) and (6) the population studied did not have any concomitant disease (such as autoimmune conditions) that would be expected to result in a distribution of *HLA-B* alleles that were different from the general population. In instances where genotype data from large cohorts of ethnically diverse individuals were reported, without respect to ethnicity, studies were only considered if one ethnicity was ≥95% of the majority. Additional studies were also included from the Allele Frequency Net Database (www.allelefrequencies.net), an online repository for HLA allele frequencies from both previously published and unpublished sources, if they met the previously described inclusion criteria. All previously published data were manually checked against the original publications to verify the *HLA-B*57:01* allele frequencies. In some cases, sample sizes or allele frequencies were updated to reflect only subjects successfully genotyped for *HLA-B*57:01* (rather than the total sample size of the study) or to correct errata in the original publication. The combined analysis included 35,630 Europeans, 1,321 South Americans, 8,570 Africans, 1,029 Middle Easterners, 3,391 Mexicans, 12,175 Asians, and 326 Southwest Asians.

2014 Reaffirmation

The guideline authors searched the PubMed database (1966 to November 2013) and Ovid MEDLINE (1950 to November 2013) for keywords ((HLA OR HLA-B OR HLA-B57 OR HLA-B*5701) AND (abacavir)), as well as a more general search for (abacavir hypersensitivity).

To construct a *HLA-B*57:01* minor allele frequency table based on ethnicity, the PubMed® database (1966 to November 2013) and Ovid

MEDLINE (1950 to November 2013) were searched using the following criteria: ((HLA-B OR HLA-B57 OR HLA-B*5701) AND (genotype OR allele OR frequency)) with filter limits set to retrieve "full-text" and "English" literature.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

2012 Original Guideline

The Clinical Pharmacogenetics Implementation Consortium's dosing recommendations are based weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account include in vitro cytokine profiling of abacavir-stimulated immune cells in patients with various *human leukocyte antigen B (HLA-B)* alleles, as well as both retrospective and prospective in vivo clinical outcome data for abacavir. Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. They have been adopted from the rating scale for evidence-based therapeutic recommendations on the use of retroviral agents.

Evidence was summarized into tables (see the "Availability of Companion Documents" field) and graded (see the "Rating Scheme for the Strength of the Evidence" field).

2014 Reaffirmation

While the guideline authors found no new evidence that would change their original recommendations, they did find one additional study that was added to the evidence table in the supplementary material (see Supplementary Table S3 in the online Supplemental material [see the "Availability of Companion Documents" field]). Recent studies have been published that further describe the mechanism by which abacavir can elicit an immune response through *HLA-B*57:01*. Discussion of these studies was added to the Supplementary Material online.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2012 Original Guideline

The authors chose to use a slight modification of a transparent and simple system with just three categories for recommendations: strong, moderate, and optional (see the "Rating Scheme for the Strength of the Recommendations" field).

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. They have been adopted from the Department of Health and Human Services rating scale for evidence-based therapeutic recommendations on the use of retroviral agents.

2014 Reaffirmation

The guideline authors reviewed recent literature and concluded that none of the evidence would change the therapeutic recommendations in the original guideline; therefore, the original publication remains clinically current.

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The evidence summarized in Supplemental Table S3 (see the "Availability of Companion Documents" field) is graded on a scale of high, moderate, and weak, based upon the level of evidence (see the "Rating Scheme for the Strength of the Evidence" field). Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

A clear benefit of *human leukocyte antigen B (HLA-B)*57:01* testing is that it leads to a reduction in the incidence of abacavir hypersensitivity reaction by identifying patients at significant risk so that alternative antiretroviral therapy can be prescribed for them. Importantly, a number of effective and safe antiretrovirals are available that can be substituted for abacavir in patients carrying this risk-related allele. *HLA-B*57:01*'s high negative predictive value (>99%) shows that it is extremely effective in identifying those at risk of immunologically confirmed hypersensitivity to abacavir.

Potential Harms

- A potential problem of *human leukocyte antigen B (HLA-B)*57:01* testing would be an error in genotyping or in reporting a genotype. This could result in high-risk patients mistakenly being given abacavir and potentially having a hypersensitivity reaction (HSR). However, given that patients testing negative for *HLA-B*57:01* also have a 3% risk of developing a clinically diagnosed hypersensitivity reaction (HSR), standard practice would include patient counseling and careful monitoring for signs and symptoms of an HSR.
- Given the lifelong nature of genotype results, an error in genotyping may also have a broader adverse impact on a patient's health care if other associations with *HLA-B*57:01* are found in the future.

Contraindications

Contraindications

If the symptoms of clinically diagnosed hypersensitivity reaction resolve after discontinuation of abacavir, drug rechallenge is contraindicated because immediate and life-threatening reactions, including anaphylaxis and even fatalities, can occur. In addition, an allergy to abacavir should be noted in the patient's medical record.

Qualifying Statements

Qualifying Statements

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

- The positive predictive value of *human leukocyte antigen B (HLA-B)*57:01* genotyping is ~50%, which means that a significant number of patients will be denied abacavir on the basis of their genotyping results even though they would have been able to take abacavir without experiencing a hypersensitivity reaction (HSR). There is currently no way to know *a priori* which *HLA-B*57:01* carriers are and which are not likely to experience HSRs, although new genetic risk factors may be found in the future. Given the potential seriousness of HSRs, the moderate positive predictive value is greatly outweighed by the very high negative predictive value of *HLA-B*57:01* genotyping.
- *HLA-B*57:01* is not predictive of any other adverse reactions a patient may experience while on abacavir treatment, nor does it predict whether abacavir will be effective in treating a patient's human immunodeficiency virus (HIV). In addition, genotyping is not a replacement for appropriate patient education and clinical monitoring for the signs and symptoms of hypersensitivity. The development of signs and symptoms of an HSR warrants that serious consideration be given to discontinuing abacavir, regardless of the *HLA-B* genotyping results.

Disclaimer

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Martin MA, Klein TE, Dong BJ, Pirmohamed M, Haas DW, Kroetz DL, Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing. Clin Pharmacol Ther. 2012 Apr;91(4):734-8. [40 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Apr (reaffirmed 2014)

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

This work was funded by National Institutes of Health (NIH) grants GM61390 and GM61374.

Guideline Committee

Not stated

Composition of Group That Authored the Guideline

2012 Original Guideline

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2014 Reaffirmation

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Financial Disclosures/Conflicts of Interest

2012 Original Guideline

The authors declared no conflict of interest.

2014 Reaffirmation

T.E.K. is a consultant for Personalis Inc. D.W.H has been a consultant to Merck. The other authors declare no conflicts of interest.

Guideline Status

This is the current release of the guideline.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) reaffirmed the currency of this guideline in 2014.

Guideline Availability

Electronic copies: Available from the Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

The following are available:

- Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B genotype and abacavir dosing: 2014 update. Clin Pharmacol Ther. 2014 May;95(5):499-500. Electronic copies: Available in Portable Document Format (PDF) from the Pharmacogenomics Knowledgebase Web site .
- Supplementary material for the 2013 update, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site .
- Supplementary material for the original guideline document, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site .
- An interactive dosing table is available from the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 15, 2013. The information was verified by the guideline developer on June 25, 2013. The currency of the guideline was reaffirmed by the developer in 2014 and this summary was updated by ECRI Institute on June 26, 2014.

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